Developing Relative Effectiveness Estimates for Medicines in Development
A Shared Framework Based on Collaboration Across Stakeholders.

Insights from the IMI GetReal Consortium

Sarah Garner  NICE
Wim Goettsch  ZIN
Mike Chambers   GSK

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115303], resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in kind contribution.

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Objectives for session

- Explain rationale and structure of IMI GetReal project
- Discuss the opportunities and challenges
Emergence of HTA

- Reimbursement decisions for new medicines now commonly driven by HTA process
- HTA paradigm set in late 1990s by early adopters (PBAC, CCOHTA, NICE...)
- Effectiveness predominantly from Phase 2-3 trials, plus meta-analysis and economic modelling (plus utilities in some countries)
- 2000s: Technical developments - meta-analysis, modelling, trial simulations....
- Networks to develop methodological (and process) standards
- Interest in aligning regulatory and reimbursement assessments where possible

**Does the paradigm fit with the emerging reality?**
Relative efficacy: the extent to which an intervention does more good than harm, under ideal circumstances, compared with one or more alternative interventions.

Relative effectiveness: the extent to which an intervention does more good than harm compared with one or more alternative interventions for achieving the desired results when provided under the usual circumstances of health care practice.

- Focus on magnitude of health benefits/harms of a (new) medicine compared with existing medicines or other technology.
- Include a comparison with the most appropriate healthcare intervention(s).
- Data derived from usual circumstances of health care practice (usually not available right after marketing authorisation)
- Present uncertainties affecting interpretation of reliability and clinical relevance of the results.

HLPF 2008b

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Challenges

‘Effectiveness’ culturally relative?
  – Choice of ‘value’ metric
  – Indirect comparisons, modelling
EBM and Evidence hierarchies
Pressures on clinical trial programmes
  – Clinical ‘footprint’, multi-country
  – External generalisability
Adaptive trial designs
Targeting: post-hoc sub-group analyses

Opportunities

Greater potential availability of RWD
‘Big data’, EHR
Advances in methods
  – Care pathways
  – Study design
  – Analysis of observational data
  – Evidence synthesis
Flexible reimbursement process (MEA...)
Networking across HTAs
Pharma response: planning early for HTA
Meeting the needs of more sophisticated stakeholders

<table>
<thead>
<tr>
<th>Phase 3a</th>
<th>Phase 3b</th>
<th>Conditional Licensing?</th>
<th>Conditional Access?</th>
<th>Phase IV “commit”</th>
</tr>
</thead>
<tbody>
<tr>
<td>“optimise”</td>
<td>“supplement”</td>
<td></td>
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</tbody>
</table>

“What combination of possible studies will provide the most valuable information to customers controlling access - in order to maximise the probability of positive access outcomes?“ What is the feasibility of the study options pre-launch and what would be required as commitments post launch? How do options reconcile with the regulatory process?”

“With all the available data, would we predict an improvement in patient outcome or care pathway efficiency over and above current practice in my healthcare system - with a reasonable level of certainty?”

“Would we accept the uncertainty for a period of time while waiting for studies to complete or for new studies to be run?”
How can ‘Real World Data’ be used earlier?

What do we mean by RWD?

**Observational**
- Non-Rx
- Rx, non-comparative
- Rx, comparative
- Rx, meta-analysis

**EHR, ‘Big’ data, database, registry, dedicated study**

**Pharma Decision making (Phase 2b, 3)**
- Understand care pathways, natural history, treatable popns
- Understand burden of illness, potential change
- Understand how effective links to (trial) efficacy
- Understand effectiveness of comparators
- Explore alternative development scenarios
- Define evidence generation (trial) programme

**Trial (RCT)**
- Adaptive designs
- Pragmatic designs/P3b

**Public (reimbursement) decisions**
- Assess relative effectiveness in reimbursed/covered popns
- Projecting effectiveness from efficacy
- Adapting efficacy/RE to reimbursed/covered popns
- Summarising/synthesising effectiveness evidence

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Pharma development pathway

Typical development pathway

- **Pre-Clin**
- **PoC 2a**: Dose range P2b → **Confirmatory P3 (x2)** → **Regulatory**
  - HEOR (obs) studies
  - Meta-analysis
  - Modelled effectiveness
  - HTA/Reimb
  - ‘Real-world’ P4
  - Regulatory safety review
  - HTA/Reimb review

Possible challenges at HTA/Reimbursement

- **P3** trials too short to capture relevant effects, need to use models
  - *Uncertainty in RE predictions*

- **P3** trials may not be able to measure factors (adherence etc.), model-based estimates unreliable
  - *RE biased*

- **P3** study population poor fit for local population/care received may not reflect HTA country
  - *RE biased*

- **P3** patient population too broad/poor fit to care pathway (targeting of therapy)
  - *Uncertainty in RE for target sub-populations*

- **P3** comparator not appropriate for local HTA: indirect meta-analysis (for RE) not robust?
  - *No credible RE estimate*

- **P3** trial event rates for comparator not in line with available RW evidence for comparator
  - *Uncertainty in RE predictions*
A continuum of evidence generation

P3a for registration & access

P3b for access

P4 including PASS, PAES, CER/RE

P4 for license and access including PAES

Conditional Licensing?

Conditional reimbursement?

Regulatory and Reimbursement reviews

Source: C Chinn
DIA Webinar July 2012

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‘Top end’ RWD = PCT
Salford Lung Study

GSK seeks real-world Relovair evidence with Salford Lung Study

Patient recruitment is expected to start this month in Salford, Greater Manchester for the first arm of a ‘real-world’ trial assessing the safety and effectiveness of Relovair, GlaxoSmithKline’s late-phase follow-up to its respiratory blockbuster Advair (salmeterol/fluticasone), in chronic obstructive pulmonary disease (COPD) and asthma.

According to GSK, the “multi-million pound” Salford Lung Study marks the first time a large, prospective, real-world trial has been conducted with a pre-licence medicine across a large population within a single geographical setting.

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Salford Lung Study

• Large Pragmatic study comparing new ICS/LABA with SoC in COPD
• Randomised, open label
• 2 arms: 50% new ICS/LABA vs 50% normal care determined by GP
• Minimal exclusions
• One year outcome: clinical exacerbations
• Powered for Superiority; N=4000
• 2 study visits (start and finish) +1 possible safety review visit
• All data captured through fully integrated EHR
• Patients from well defined local NHS area with a strong academic centre
• Study drug supplied through local pharmacies
• Safety through EHR monitoring with 1 visit

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Linked Primary & Secondary Care Data Sources

Vision
Emis

GP

GP

GP

GP

Hosp.

Nurses

Demographics, Patient reporting

Data Repository in PCT

Real-time

Person-identifiable and sensitive information removed

Anonymised Data Repository in PCT

24-hourly updates

Trusted person poses question(s)

Sense-making software & support

F I R E W A L L
Decision making
Toleration of uncertainty

Actual RW performance

Ability at launch to predict relative effectiveness

Customer uncertainty threshold

RCTs for Registration

RCTs optimised

RCTs optimised and supplemented with PIIIb effectiveness study

With Phase IV effectiveness study commitment

Development strategy

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Non-RCT evidence

3.2.8 Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. The problems of confounding, lack of blinding, incomplete follow-up and lack of a clear denominator and endpoint will usually be much worse in non-randomised studies than in RCTs. But in some circumstances, evidence from these studies will be needed in addition to RCT data, in particular to estimate relative treatment effect over longer time horizons or to measure particular outcomes that have not been included in the RCTs. In the absence of valid RCT evidence, evidence from studies least open to bias will be considered preferentially with reference to the inherent limitations of the specific design.

3.2.9 Inferences about relative treatment effects drawn from non-RCT evidence will necessarily be more circumspect than those from RCTs with properly controlled evidence. The bias that may be present in non-randomised data means the results should be interpreted cautiously. When possible, the use of more than one independent source of such evidence needs to be examined to gain some assurance of the validity of any conclusions drawn.

3.2.10 Whatever the sources of evidence available on a particular technology and patient group, they will be integrated into a systematic review with explicit, valid and replicable methods (see section 5.3).
Role of real-world data uncertain (EMA developing guideline)

- EU/EMA: new pharmacovigilence legislation - efficacy studies/PAES
- Continuing Interest in Benefit Risk
- Adaptive licensing (?bridge to parallel discussions in HTA, Managed Entry etc)

How Regulatory Agencies could interact with Health Technology Bodies, Source:
Lonnongren et al DIA, Berlin, March 2009
Adaptive Pathways

- Current model (a):
  - Single authorisation decision point
  - Pre-authorisation focus on RCTs
  - Rapid expansion of treated population after MA
  - Treatment experience contributes little to evidence generation

- Adaptive licensing (b):
  - Potentially earlier “initial” MA and/or MA based on fewer patients
  - Prescribing restrictions slow expansion of treated population
  - Greater use of observational studies to capture “effectiveness” data
  - Cycles of evaluation and label modification

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### Sources
- AHRQ Registry of Registries
- NEWDIGS On market data
- Clinical trials . gov

### Initiatives
- TAPESTRY
- Green Park
- PCORI Initiatives
- OMOP / Sentinel
- EU transparency
- EU pharmacovigilance (PAES)

### Methods
- ISPOR methods
- GRACE (critical appraisal)
- AHRQ Handbook
- CER

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Universitair Medisch Centrum Utrecht, the Netherlands
Academisch Ziekenhuis Groningen, the Netherlands
Zorginstituut Nederland, the Netherlands
European Medicines Agency, UK
European Organisation for Research and Treatment of Cancer, Belgium
Haute Autorité de Santé, France
London School of Hygiene and Tropical Medicine, UK
National Institute for Health and Care Excellence, UK
Panepistimio Ioanninon, Greece
Universität Bern, Switzerland
University of Leicester, UK

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LA Santé Epidemiologie Evaluation et Recherche, France

Patients’ organisations
International Alliance of Patients' Organizations, UK

EFPIA companies
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Boehringer Ingelheim International GmbH, Germany
Bristol Myers Squibb EMEA sarl, US
Eli Lilly, UK
F. Hoffmann-La Roche AG, Switzerland
Janssen Pharmaceutica NV, Belgium
Merck KGaA, Germany
Merck Sharp & Dohme Corp., US
Novartis Pharma AG, Switzerland
Novo Nordisk A/S, Denmark
Sanofi-Aventis Research and Development, France
Takeda Development Centre Europe Ltd, UK

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The adoption of real world / relative effectiveness objectives in a pre-authorisation development programme creates many operational, methodological, regulatory, and ethical issues.

There is little guidance on how to incorporate alternative study designs into a development programme to optimally meet the needs of all stakeholders over time; and Pharmaceutical R&D organisations need more certainty as to:

• The cost and feasibility of real world / relative effectiveness designs
• The value of different programmes to HTA bodies and other healthcare decision makers;
• The best balance of pre-launch and post-launch effectiveness research and
• The impact of innovative development choices on the regulatory review process and subsequent post-authorisation commitments.

Source: GetReal Project proposal, June 2013
GetReal Objectives

Aim: to advance understanding and have a lasting impact in this area through:

- Bringing together regulators, HTA bodies, companies, academia/health care professionals, patients and other societal stakeholders
- Developing common use of terminology and taxonomy
- Critically assessing existing processes, methodologies, and key research issues
- Proposing innovative (and more pragmatic) trial designs and assessing the value of information that might be provided
- Assessing operational, ethical, regulatory issues: proposing and testing solutions
- Proposing & testing innovative data-analytical, predictive modelling approaches
- Creating new decision making frameworks for R&D and in Sci Advice processes
- Providing open tools for use in implementing development programmes and in the assessment of the value of new medicines, incl. devt of user friendly software

Source: GetReal Project proposal, June 2013
GetReal Objectives

- **Recommendations**  Directly engaging organisations and individual experts involved in ongoing policy discussions; understanding how to evolve processes in a coordinated way without unnecessarily raising burden of evidence generation and avoiding unintended consequences.

- **Alignment**   Encouraging alignment of existing & future policy recommendations, frameworks and tools by, among others, pharma companies, regulatory authorities, HTA/reimbursement agencies, clinicians and patient organizations.

- **Research agenda**  Developing an agenda for future research to ensure the continuation of work and sustainability of the project.

- **Training**  Developing training activities (both directly and through outreach to other ongoing educational initiatives including EU2P, Pharmatrain, EUnetHTA and academic programmes) for researchers, healthcare decision makers and societal stakeholders in public and private sectors - increase knowledge of relative effectiveness concepts and how best these can be applied.

*Source: GetReal Project proposal, June 2013*
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Flow of work

Internal validity
- RCTs (phase II)
- RCTs (phase III)
- Pragmatic RCTs
- Cohort studies

External validity
- Clinical databases

Tasks
1) Identify suitable case-studies
2) Assess patient characteristics and risk of bias
3) Re-analyze individual patient data if available
4) Obtain best estimates of RE for different patient groups
5) Predict RE and absolute benefits and harms in different patient groups
6) Develop user-friendly software
7) Develop guidance and recommendations

Data management, analysis and decision support software
- Statistical package
- Statistical package

Network meta-analysis and meta-regression analysis

Assessment of studies and re-analysis where applicable

Mathematical simulation model

Guidance and recommendations

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WP1
Frameworks
Processes
Policies

WP2
Understanding the efficacy-effectiveness gap
simulation of trials to improve design

WP3
Overcoming practical barriers to the design of real-world studies

WP4
Identifying best practice and creating new methods for evidence synthesis and predictive modelling

5 Case studies using drugs that had difficulty at regulation and HTA
- 360 degree reviews
- Re-designing development pathways to include real-world data
- Simulation
- Ascertaining impact on decision makers

- Standardising terminology
- Interviews to understand and the perspectives and policies of different stakeholders
- Designing a framework for decision-making during development
Developing a framework for the assessment of development strategies that provide evidence of relative effectiveness

- Develop an agreed glossary of different types of study designs that considers study attributes and suitability for different applications.
- Identify stakeholder policy and perspectives with respect to alternative study designs.
- Identify and engage with other related initiatives, either EU-wide or in individual member states or internationally.
- Predict the impact of the inclusion of alternative study decisions on the decision-making processes of industry, regulators and HTA agencies (case study simulations)
- Support subsequent policy development: develop and pilot a framework for assessing options for the inclusion of non-standard study designs in development strategies
Aim: Create a shared platform for the inclusion of alternative study designs in drug development and drug assessment strategies.

**Stakeholder Mapping**
- Track stakeholders approached and interviews of stakeholders planned by GetReal members to avoid duplication of efforts.

**Review of Policies and Perspectives on RWD**
- Eight stakeholder groups (e.g. HTA, industry, academia)
- Ongoing interviews and literature review

**GetReal Glossary**
- Developing a common understanding of terms and definitions for use by GetReal participants and wider scientific community

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WP1 Case Studies
Redesigning the Development Pathway

Information Sources
- Publicly available documents (reg, HTA)
- Stakeholder interviews
- Company commentaries & presentations
- Original company source documents

Workshop 1
(360° review)
Outputs
- Discussion summary / minutes
- Key scientific questions (sources of bias and uncertainty in RE)
- Alternative development design options using real-world evidence

Workshop 2
Outputs
- Discussion summary / minutes
- Stakeholder insight & reactions to potential options
- Scenario summary
- Contribute to decision framework
- Publications

Summaries

Simulations

Pilot already underway (multiple sclerosis)
Five full case studies to follow, first one to commence end of this year

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WP1 Case Study Selection Criteria

Essential
• Effectiveness challenge(s) for recent medicine from HTA
• Potential for RWD to improve effectiveness estimates.
• Feasible to use medicines in Case Study:
  – Insights into the company’s decision-making can be provided by people who were involved in the process and/or
  – Data can be made available by the company, enabling the company’s decision-making relating to trial design and data generation to be analysed

Desirable
• Disease area and the relative effectiveness challenge(s) are relevant for future submissions and appraisals.
• Disease area/medicine is of interest to GetReal stakeholders, in particular the EFPIA partners.
• Issues addressed in the case study can be applied to other disease areas
• Case study can be used across the GetReal project (i.e. as a case study for other Work Packages).
## Recent NICE appraisals

<table>
<thead>
<tr>
<th>TA 232</th>
<th>Retigabine for the adjunctive treatment of partial onset seizures in epilepsy.</th>
<th>Clinical trials mandated forced (protocol-driven) titration rather than titration tailored to individual patient as is seen in practice.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TA278</td>
<td>Omalizumab for treating severe persistent allergic asthma (review of TA 133 and 201).</td>
<td>Observational data used for extrapolation of treatment effect and for HRQoL in children amongst other things.</td>
</tr>
<tr>
<td>TA279</td>
<td>Vertebral fractures – Vertebroplasty and kyphoplasty</td>
<td>Observational data used by committee to accept mortality benefit (however committee could not use the data to quantify it).</td>
</tr>
<tr>
<td>TA283</td>
<td>Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion</td>
<td>Observational data used by committee to assess safety compared with unlicensed bevacizumab, however committee stopped short of using it for cost-effectiveness analysis.</td>
</tr>
</tbody>
</table>
## Use of non-RCT data for estimating clinical efficacy in modelling

<table>
<thead>
<tr>
<th>TA</th>
<th>Condition/Drug</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>TA 151</td>
<td>Diabetes – Insulin pumps</td>
<td>Clinical efficacy from a registry – Insulin Pumps Clinical database - much larger, of longer duration and more representative of people likely to be considered for CSII therapy in routine clinical practice than the populations in the RCTs available</td>
</tr>
<tr>
<td>TA 165</td>
<td>Organ preservation (renal) - machine perfusion and static storage</td>
<td>Prospective cohort study and multi-national registry study used for efficacy in model</td>
</tr>
<tr>
<td>TA 166</td>
<td>Hearing impairment - cochlear implants</td>
<td>Baseline risk of operative mortality in model, other parameters in modelling as judged most appropriate source</td>
</tr>
<tr>
<td>TA 185</td>
<td>Soft tissue sarcoma – trabectedin</td>
<td>Three uncontrolled phase II trials of trabectedin</td>
</tr>
<tr>
<td>TA 188</td>
<td>Human growth hormone (somatropin) for the treatment of growth failure in children (review)</td>
<td>Kabi International Growth (KIGS) observational database</td>
</tr>
<tr>
<td>TA 202</td>
<td>Chronic lymphocytic leukaemia – ofatumumab</td>
<td>NO RCT- conditional license</td>
</tr>
<tr>
<td>TA 209</td>
<td>Gastrointestinal stromal tumours (unresectable/metastatic) – imatinib</td>
<td>One non-randomised retrospective cohort study</td>
</tr>
<tr>
<td>TA 241</td>
<td>Leukaemia (chronic myeloid) - dasatinib, nilotinib, imatinib (intolerant, resistant)</td>
<td>Twelve studies were observational (seven of dasatinib, four of nilotinib and one retrospective study of both) three single-arm studies of high-dose imatinib – available RCTs were of poor quality</td>
</tr>
</tbody>
</table>
## WP1: Review of HTA outputs: NICE

### Appraisals using non-RCT data for some parameters in model

| TA 167 | Abdominal aortic aneurysm - endovascular stent-grafts | Large registries of relevance to UK practice - baseline risk of operative mortality in model, other parameters in modelling as judged most appropriate source |

### Appraisals using non-RCT data for longer term effectiveness

| TA 177 | Eczema (chronic) – alitretinoin |
| TA 211 | Constipation (women) – prucalopride |
| TA 221 | Thrombocytopenic purpura – romiplostim |
| TA 247 | Rheumatoid arthritis - tocilizumab (rapid review TA198) |
| TA 293 | Thrombocytopenic purpura – eltrombopag (review) |

### Other uses of non-RCT data in appraisal

| TA 238 | Arthritis (juvenile idiopathic, systemic) – tocilizumab | observational study of 146 patients - adjustment factor - difference in the proportion of responders between the total population with JIA and the subpopulation with systemic JIA. Used to correct for ACR response rates in the indirect comparison |

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WP1: Testing out different strategies and pathways

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Evidence Generation</th>
<th>Evidence Synthesis</th>
<th>Reg/reimb decision making</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual</td>
<td>TRIALS A AND B</td>
<td>Pivotal</td>
<td>EMA: Dossier</td>
<td>-</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>NICE: C-U</td>
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<tr>
<td>Alternative1</td>
<td>AMEND TRIAL B</td>
<td>As Actual</td>
<td>As Actual</td>
<td>Costs ↔ Uncertainty ↑</td>
</tr>
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<td>Timescale ↔ Acceptability ↓</td>
</tr>
<tr>
<td>Alternative2</td>
<td>As Actual</td>
<td>INTRODUCE NMA (+ RWE)</td>
<td>As Actual</td>
<td>Costs ↔ Uncertainty ↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Timescale ↔ Acceptability ↓</td>
</tr>
<tr>
<td>Alternative3</td>
<td>AMEND TRIAL B</td>
<td>INTRODUCE NMA (+ RWE)</td>
<td>Control Arms of RCTs + Registry</td>
<td>Costs ↔ Uncertainty ↓</td>
</tr>
<tr>
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<td>Timescale ?↔ Acceptability ↓</td>
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</tbody>
</table>

Source: GetReal WP1 Keith Abrams

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WP1: Towards a new Framework

• A set of guiding principles which lay out what success looks like
• A taxonomy that links methods to R&D and regulatory/HTA decision-making and tolerance
• A framework which is adaptive to changes in landscape and built with broader engagement
• Guidance which supports R&D planning, strategy and scientific exchange
• Final output of research into methods (by GetReal partners) in the form of guidance
• *Creation of an observatory that keeps track of best practice and ongoing changes in regulatory/HTA landscape*
Case studies, case studies, case studies..
Perspectives on RWD and GetReal
• HTA
• Regulatory
• Industry
• ...Others?
**Input from Pharma Industry Partners**

**Workshop 1**

**Insights**
- Clinical development programme (*recent medicine*)
- Views on Reg/HTA response (*'effectiveness challenge'*)
- Post-launch evidence generation (*RWD*)

**Simulations**
- Full trial data (medicine vs comparator)
- Partial trial data (single arm of trial, treatment ‘anonymised’)
- Aggregate trial data (? With *de novo* in-house analysis)

**Data: trial**
- Comparative obs. data on medicine vs... (*phase 4, registry*)
- Non-comparative obs. data on medicine (*registry, burden*)
- Disease area data: natural history/epi (inc-prev)/burden

**Data: non-trial**
- Access: collaborating organisations
- Access: technical skills (epi/stats/HEOR) in-house
- Synthesis: Statistical models, (incl meta-analysis)
- Synthesis: Disease or economic models

*subject to proposal and development of protocol for analysis of data , to be finalised after Workshop 1*

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Questions for discussion
Questions

What is your understanding of ‘RWD’?

What is your organisation’s view on early use of RWD?

What might be the impact of (earlier) use of RWD? What would be the challenges?
When evaluating the impact of early use of RWD, what needs to be considered?
What would you like to see in a new decision-making framework?
How can GetReal add most value?
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The End

Thank you for your participation